REMARKS

Status of the Claims

Claims 13-24 are currently pending and under examination. Claims 1-12 and 25 have been canceled without prejudice or disclaimer to the subject matter claimed therein.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 13-24 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to distinctly point out and claim the subject matter regarded as the invention.

The Advisory Action of January 27, 2010, stated that Applicants response of January 14, 2010 had overcome the basis for this rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 13-24 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious under Wangh (U.S. Patent 6,753,457) in view of Samocha-Bone (Molecular Human Reproduction 4: 133-137, 1998).

The Office Action alleges that it would be obvious to combine the methods of reprogramming nuclei in somatic cells as disclosed by Wangh with the methods for treating sperm nuclei disclosed in Samocha-Bone to arrive at the claimed invention.

The Office Action acknowledges that Wangh does not disclose use of polyanions without the use of CSF. The Office Action however alleges that at the time of filing the present application, the use of polyanions to cause chromatin decondensation to allow DNA to bind to maternal histones was known.

Applicants respectfully disagree that one skilled in the art could arrive at the claimed invention through any combination of these references. Wangh teaches products and methods for causing non-dividing nuclei to activate (*i.e.*, to go through one or more steps of nuclear activation) (Wangh at Col. 2 ln. 21-23). Wangh does not actually describe any method of how to reconstitute an embryo using a treated somatic nucleus and an enucleated oocyte and that even the vague outline provided by Wangh relates to Xenopus embryos for which the use of xenopus egg extracts would be expected to have some effect. In Wangh, each method described uses purified egg extracts to induce and so study various aspects of nucleus biology and behaviour. Preferably, these egg extracts come from Xenopus eggs (Wangh at Col. 4 ln. 55-56). Wangh

does not teach any method to reconstitute a mammalian embryo, which is the subject of the claimed invention. The claimed invention is a method to reconstitute an embryo which behaves as a normal embryo and undergoes development and cycles of cell division directed by the introduced somatic nucleus and which can develop into a complete organism. No data are presented in Wangh to support the proposed cloning method described in section IX at col. 31 ln. 20 to col. 32 ln. 30. In any event, Wangh is limited to Xenopus which is not a mammal and therefore not within the scope of the claimed invention.

The examiner has previously argued and continues to argue that one skilled in the art in reading to Wangh would formulate a method in which a nucleus is not treated with an egg extract. Applicants find it this an incredulous assertion, as the entire crux of the Wangh patent is to extol the use of egg extract. All the examples in Wangh teach the use of such extracts, and every claim of Wangh features the egg extracts. One skilled in the art could only interpret that the egg extract is an essential element in the methods of Wangh, and therefore one skilled in the art would have absolutely no reason to omit it. It can only be through impermissible hindsight in reading the currently claimed invention and observing the these extracts. Only through reading the currently claimed invention can one skilled in the art realize that the egg extract is non-essential. The particular steps of the claimed invention were not known or obvious in the art prior to Applicants present application that demonstrates showed that such a combination of steps as claimed in claim 13 a successful reconstitution of a non-human mammalian embryo. That people in the art were interested in reconstituting embryos is similarly not disputed, but no one developed or suggested that the claimed method of claim 13 could be used to achieve this goal.

The Advisory Action reiterates an argument that the use of closed claim language ("consisting of") does not mean that the removal of an additional feature present in a prior art reference may not be obvious. Applicants respectfully disagree that such an argument is applicable to the claimed invention. The claimed method is explicitly contrary to the teachings of the cited references. The claimed invention is directed to fully reconstituting a mammalian embryo. Conversely, Samocha-Bone is a method of decondensing sperm for flow cytometry analysis and Wangh is a method of nuclear reprogramming Xenopus oocytes. When one skilled in the art departs from the explicit teaching of the art, omission of an additional feature can no longer be routine experimental practice, but instead is an inventive step, or conversely, it cannot

be considered obvious to alter the teaching of the prior art so as to arrive at a claimed invention if this goes against the explicit teaching of the prior art. Accordingly, the omission of features in the claimed invention cannot simply be regarded as routine.

With regard to the cited references, the Advisory Action apepars to find that the use of the polyanion heparin, used in combination with a reducing agent such as GSH (reduced glutathione), was known in to induce nuclear swelling in sperm, and further that the cited art documents of Lasselle and Reyes teach that heparin alone is able to cause nuclear decondensation of sperm nuclei. Applicants note that the reference of Delgado is a later publication that when the present application was filed, and would therefore not be available to one skilled in the art trying to arrive at a method of reconstituing an embryo.

Firstly, Applicants respectfully reiterate as stated above that that selection of a polyanion and the non-selection of a reducing agent is not obvious from these prior art references. Simply, one skilled in the art interested in reconsitituting a mammalian embryo would require a reason to omit the reducing agent, and such a reason is not apparent from any cited reference. Further, Applicants respectfully disagree with the assumption that data from the decondensation of haploid sperm nuclei would be used by one skilled in the art when devising a protocol to treat somatic diploid nuclei. As stated previously, significant differences exist between somatic diploid cells and haploid sperm. One skilled in the art would require first a reason to utilize a method for treating a somatic cell with a method of treating a haploid cell and further then decide that a feature in the method was now unnecessary. Accordingly, Applicants respectfully assert that one skilled in the art cannot arrive at the claimed invention based on the cited references.

Morever, the reference of Lasselle is a study of the nuclear decondensation effects upon human spermatozoa of heparin, GSH and mixtures thereof, and the reference of Reyes is a study into bull sperm membrane stability using an array of fluorescent probes (sperm were subjected to various conditions including incubation with heparin, GSH, SDS (sodium dodecyl sulphate), Triton X-100 and certain combinations of these reagents). Both Reyes and Laselle teach that either GSH or heparin or SDS or Triton X-100 can lead to sperm nuclear decondensation (see Table I, Reyes and Table 1, Lasselle). These reagents and combinations of these reagents have different levels of efficiency in causing sperm nuclear decondensation both over time and between species. For instance, according to Reyes and with reference to Table I therein, GSH causes higher levels of sperm nuclei decondensation immediately following addition (T_0) and in

the following 3 hours. It is only at the next recorded time point (after 22 hours) that heparin shows higher levels of decondensation than GSH according to Reyes. Likewise, combinations of heparin and GSH, according to Reyes, cause higher levels of nuclear decondensation following addition and after 1, 2 and 3 hours. In significant contrast, as demonstrated in the working examples, isolated somatic nuclei are incubated with the polyanion until swelling occurs, which takes between 30 to 60 minutes (*see*. page 6 final paragraph of the present specification). Accordingly, one skilled in the art wanting to induce nuclear decondensation over a short time period would have logically utilized either GSH alone or a combination of GSH and heparin to induce nuclear decondensation. Further, while Lassalle (and Table 1 therein) show a different correlation between the relative effects of GSH versus heparin (specifically a higher level of decondensation for heparin treatment alone versus GSH treatment alone after 1 hour), Lasselle demonstrates that a combination of GSH and heparin results in higher levels of sperm nuclei decondensation than either reagent alone after 1 hour.

Further, with regard the discrepancies apparent to one skilled in the art in comparing Lasselle and Reyes, one skilled in the art may recitify that these differences are due to: the different concentrations of reagent used in these two studies; or differences between human and bovine sperm or that one of the data sets was incorrect due to a flawed experimental design or due to the inaccurate recording of the results. One skilled in the art would, however, readily conclude that based upon both of these prior art documents, that a combination of GSH and heparin is the most efficient means of inducing nuclear swelling, and therefore if induction of nuclear swelling is desired that a combination of the reagents is obviously preferred.

Accordingly, the fact that the claimed invention only uses a polyanion to induce nuclear swelling contradicts the teachings of Reyes and Lasselle. For one skilled in the art to have utilized a far less efficient option (*i.e.*, polyanion treatment versus treatment with a combination of a reducing agent and a polyanion) is not obvious, and it can only be after one has knowledge that such a choice allows for reconsitution of a mammalian embryo that this aspect of the invention seems so simple and thus is viewed as obvious.

To summarize, the claimed invention is directed to a method of fully reconstituting a mammalian embryo. The steps that one skilled in the art man would have had to take therefore to modify the teaching of Wangh so as to arrive at the claimed method are: firstly, to reason that an amphibian oocyte and a non-human mammalian oocyte are interchangeable; secondly, to

reason the xenopus egg extracts used in all the methods according to Wangh are unnecessary; thirdly, to reason that although inducing nuclear swelling is necessary, the use an egg extract to induce swelling as described by Wangh can be achieved with use of only a polyanion such as heparin, even though the art teaches that polyanions are useful for haloid cells, as compared to somatic diploid cells, and that combinations of a polyanion and a reducing agent induce better levels of nuclear swelling than a polyanion or reducing agent alone. Simply, one skilled in the art wishing to reconsitute a mammalian embryo has no reason to make the changes in methods that are directed to achieveing far different outcomes and reasonably expect to be able to arrive at the claimed invention.

It is therefore requested that the obviousness rejections are withdrawn and that the present Patent Application is allowed to proceed to grant.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, she is invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP

/Zachary Derbyshire/

Zachary Derbyshire
Registration No. 64,669

Dated: **June 14, 2010**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
202-739-3000